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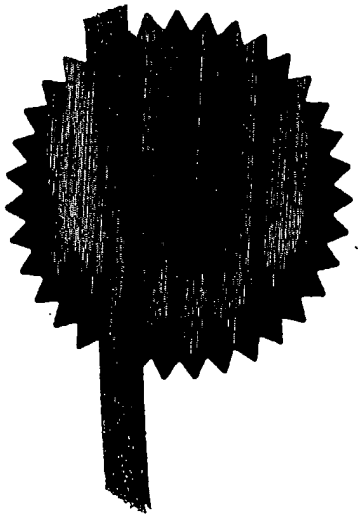

Signed P. Mahoney

Dated 19 June 2001

Patents Form 1/77

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1/77

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P01/7700 0.00-0030305.7

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 000217 /GB

2. Patent application number *(The Patent Office will fill in this part)* — **0030305.7** — 13 DEC 2000

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Eli Lilly and Company
Lilly Corporate Center
Indianapolis
Indiana 46285
USA

Patents ADP number *(if you know it)*

428904002 IS

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of invention — COMPOUNDS

5. Name of your agent *(if you have one)*

MARTIN ALEXANDER HAY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

13 QUEEN VICTORIA STREET
MACCLESFIELD
CHESHIRE
SK11 6LP

Patents ADP number *(if you know it)*

[redacted]001 7710858001 IS

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body
See note (d))

No

COMPOUNDS

This invention relates to compounds which are inhibitors of serine proteases and to pharmaceutical compositions thereof and their use in the treatment of the human or animal body.

The serine proteases are a group of proteolytic enzymes which have a common catalytic mechanism characterized by a particularly reactive Ser residue. Examples of serine proteases include trypsin, tryptase, chymotrypsin, elastase, thrombin, plasmin, kallikrein, Complement C1, acrosomal protease, lysosomal protease, cocoonase, α-lytic protease, protease A, protease B, serine carboxypeptidase II, subtilisin, urokinase, Factor VIIa, Factor IXa, and Factor Xa. The serine proteases have been investigated extensively over a period of several decades and the therapeutic value of inhibitors of serine proteases is well understood.

Serine protease inhibitors play a central role in the regulation of a wide variety of physiological process including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. It is well known that these compounds inhibit a variety of circulating proteases as well as proteases that are activated or released in tissue. It is also becoming clear that serine protease inhibitors inhibit critical cellular processes, such as adhesion, migration, free radical production and apoptosis. In addition, animal experiments indicate that intravenously administered serine protease inhibitors, variants or cells expressing serine protease inhibitors, provide a protective effect against tissue damage.

Serine protease inhibitors have also been predicted to have potential beneficial uses in the treatment of disease in a wide variety of clinical areas such as oncology, neurology, haematology, pulmonary medicine, immunology, inflammation and infectious disease.

In particular serine protease inhibitors may be beneficial in the treatment of thrombotic diseases, asthma,

emphysema, cirrhosis, arthritis, carcinoma, melanoma, restenosis, atheroma, trauma, shock and reperfusion injury.

Thus for example an inhibitor of Factor Xa has value as a therapeutic agent as an anticoagulant, e.g. in the treatment and prevention of thrombotic disorders. The use of a Factor Xa inhibitor as an anticoagulant is desirable in view of the selectivity of its effect. Many clinically approved anticoagulants have been associated with adverse events owing to the non-specific nature of their effects on the coagulation cascade.

Also, there are well-known associations of α1 protease inhibitor deficiency with emphysema and cirrhosis and C1 esterase inhibitor deficiency with angioedema.

It has now been found that certain aromatic compounds carrying bulky lipophilic side chains are particularly effective as inhibitors of serine proteases, especially proteases with negatively charged P1 specificity pockets, and most especially the serine proteases thrombin, and most importantly Factor Xa. The Factor Xa inhibitors of this invention are potentially useful for the prophylaxis or treatment of thrombotic disorders such as amongst others venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction, and cerebral thrombosis. They potentially have benefit in the treatment of acute vessel closure associated with thrombolytic therapy and restenosis, e.g. after transluminal coronary angioplasty or bypass grafting of the coronary or peripheral arteries and in the maintenance of vascular access patency in long term hemodialysis patients.

Factor Xa inhibitors of this invention may, with benefit, form part of a combination therapy with an anticoagulant with a different mode of action or with a thrombolytic agent.

It has been reported in WO99/11658 and WO99/11657 that certain benzamidine and aminoisoquinoline derivatives carrying a bulky lipophilic side chain are excellent inhibitors of serine proteases. Unfortunately, it has since been found that

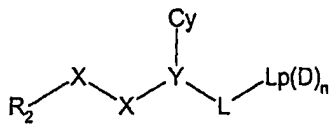
benzamidine compounds of WO 99/11658 in general demonstrate poor oral bioavailability.

Surprisingly, it has now been found that certain other aromatic compounds also show inhibitory activity against serine proteases, in particular Factor Xa, despite the lack of the amidino or 1-aminoisoquinoline functionality previously believed to be crucial for activity as a factor Xa inhibitor. Many of these compounds also possess other structural features that further distinguish them from the compounds of WO99/11658 and WO99/11657.

Where compounds of the invention have been tested, they have generally demonstrated superior oral bioavailability in comparison with benzamidines disclosed in WO 99/11658. Also, it has been found that the compounds of the invention perform excellently in the prothrombin time assay (PT) when compared to aminoisoquinolines of similar factor Xa activity and structure. The PT assay is a coagulation assay and it is widely accepted that direct acting Factor Xa inhibitors which perform well in the PT assay are more likely to be good antithrombotics.

In WO99/09053 certain 2-aminobenzamide compounds are disclosed as potential motilin receptor antagonists and in US 3268513 similar 2-aminobenzamide compounds are suggested as potential antibacterial agents. However, the novel compounds of the present invention have not before been suggested as potential serine protease inhibitors.

Thus viewed from one aspect the invention provides a serine protease inhibitor of formula (I):



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally

interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachement of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 or 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

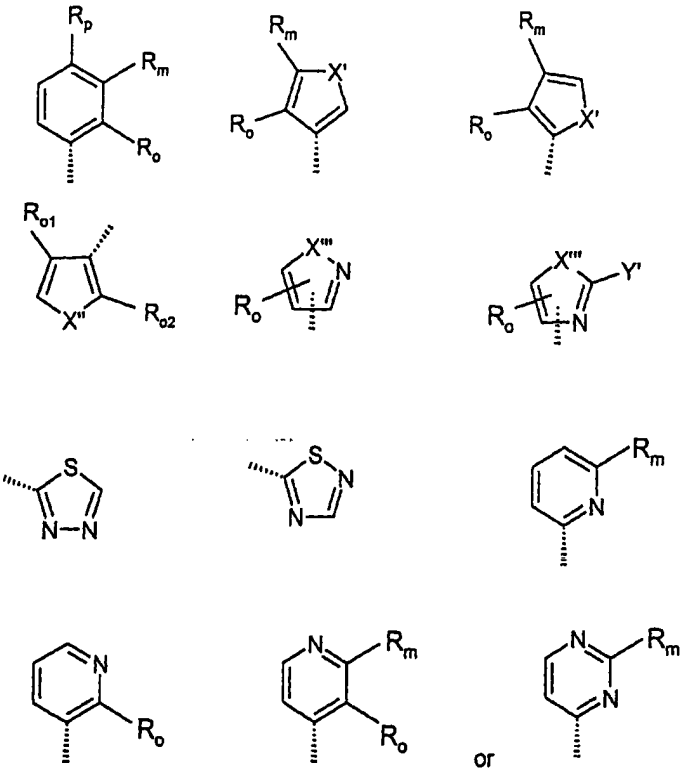
Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R_{3a} or $R_{3i}X_i$;

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms

42. A compound according to any one of claims 1 to 39 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy) and $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group).

43. A compound according to any one of claims 1 to 39 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

44. A compound according to any one of claims 1 to 39 wherein Cy is selected from:



wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

R_p is selected from hydrogen and fluoro; or

R_o and R_m or R_m and R_p form an $-OCH_2O-$ group; or

R_o and R_m together with the ring to which they are attached

form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur);

one of R_{o1} and R_{o2} is hydrogen and the other is R_o;

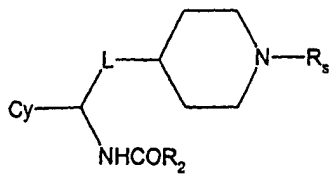
45. A compound according to any one of claims 1 to 37 wherein Cy is selected from phenyl (optionally substituted by methyl, ethyl, prop-2-yl, phenoxy, hydroxy, ethoxy, benzyloxy, prop-2-yloxy, nitro, amino, acetylamino, methylsufonylamino, dimethylamino, chloro, methoxy, trifluoromethyl, methylthio, methylsulfonyl, tert-butylthio, tert-butylsulfonyl, aminosulfonyl or carbamoyl), pyridyl, thienyl, furanyl, imidazolyl, thiazolyl (optionally substituted by amino), napththyl, isoquinolinyl and quinolinyl.

46. A compound according to any one of claims 1 to 37 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5yl, naphthyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl, and quinolin-8-yl.

47. A compound according to any one of claims 1 to 37 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5yl and quinolin-4-yl.

48. A compound according to any one of claims 1 to 37 wherein Cy is selected from phenyl, 2-methoxyphenyl, 4-carbamoylphenyl and pyrid-2-yl.

49. A compound of the formula:



wherein Cy, R_2 and R_8 are as defined hereinabove in any preceding claim and L is CONH, CH_2NHCO, $CONHCH_2$, $CONHCH_2CH_2$ or $CON(Me)CH_2$.